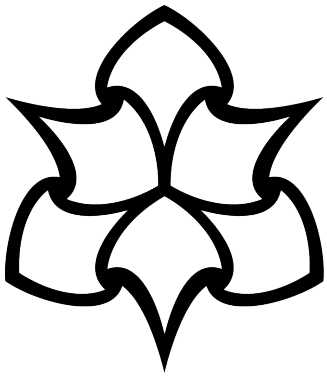

The Impact of Pneumococcal Conjugate Vaccines on Invasive Pneumococcal Disease

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The Impact of Pneumococcal Conjugate Vaccines on Invasive Pneumococcal Disease

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Declaration

I, Godwin Oligbu, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed:

Date:

Abstract

The UK introduced the 7-valent pneumococcal conjugate vaccine (PCV7) into the national childhood immunisation programme in 2006, which was replaced with the 13-valent PCV (PCV13) in 2010. The published articles presented in this thesis assessed the impact of PCVs on invasive pneumococcal disease (IPD) especially in children and those with underlying comorbidities, particularly sickle cell disease (SCD).

The systematic review of PCV failures found a low incidence of vaccine failures irrespective of the PCV used in the national immunisation programme. After PCV7 introduction, serotypes 19F and 6B were responsible for more than two-thirds of vaccine failure cases. In keeping with published studies, these serotypes were also responsible for most cases of vaccine failure in the national surveillance of PCV failures in England and wales before the introduction of PCV13. After PCV7 was replaced with PCV13, serotypes 3 and 19A were over-represented among the vaccine failure cases. Overall case fatality rate (CFR) in children with PCV failure was low, with only six of 161 children (4%) dying, including five (83%) who had significant underlying comorbidities.

A review of IPD in children with SCD however identified continued increased risk of IPD in children with SCD. The overall CFR among published cases was 11.5%. More than half of the serotypes associated with IPD were not included in the PCV13, of which more than half were due to serogroup 15. Similarly, in the enhanced national surveillance of IPD in children with SCD, in England, it was identified that there were 881 IPD cases, including eleven children homozygote for haemoglobin S (HbSS) and one double heterozygote for haemoglobin S and C (HbSC). Children with SCD remained 49 times more likely to develop IPD and 5 times more likely to die of their infection compared to their healthy peers. Most IPD cases in SCD were also due to serotypes that were not covered by PCV13, particularly serogroup 15, and this finding was found to be consistent with published literatures.

Research was also carried out to determine the epidemiology of pneumococcal meningitis following the introduction of PCV in England and Wales. The incidence of pneumococcal meningitis did not change after PCV7 introduction, but declined by 48% after the vaccine was replaced with PCV13 in keeping with large reductions in cases due to the additional PCV13 serotypes 7F and 19A. Currently, meningitis due to PCV13 serotypes is rare and the

non-PCV13 serotypes 8 and 12F are the predominant causes of pneumococcal meningitis. Additionally, while the incidence of pneumococcal meningitis has declined, the CFR has remained high at 17.5%. However, childhood CFR for IPD remained low at 4.8%, with more than half (59%) of deaths occurring in infants, mainly in those aged <3 months who accounted for 28% of all fatal cases. Overall, 35% of children who died had underlying risk factors for IPD while meningitis was responsible for 47% of IPD-related deaths.

In summary, this thesis has demonstrated that the rate of PCV failure, irrespective of the vaccine used or schedule, was very low, as was CFR in children with PCV failure. Most children with PCV13 failure were healthy, developed LRTI, and survived their infection without long-term complications. The continuing low prevalence of PCV7 failures after PCV13 introduction is reassuring and it is likely that PCV13 failure will also decline in the coming years. However, children with SCD remained at risk of IPD and death despite these measures of daily penicillin prophylaxis as well as pneumococcal vaccination. The majority of serotypes causing IPD in SCD are no longer vaccine preventable, therefore every effort should be made to ensure that these children adhere to penicillin prophylaxis and pneumococcal vaccines.

Thus, in conclusion, PCVs are highly effective in preventing IPD due to the respective vaccine serotypes. The childhood pneumococcal vaccination programme has led to a significant reduction in the incidence of IPD, including meningitis. However, compared to other clinical presentations, there was a lower than expected impact on pneumococcal meningitis, with case fatality rates due to meningitis remaining relatively unchanged across the age groups. Given that most IPD cases, including meningitis are now due to non-PCV13 serotypes, including most fatal IPD cases, additional strategies need to be introduced to reduce childhood pneumococcal deaths in countries with established pneumococcal vaccination programmes.

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Abbreviations

ACIP: Advisory Committee on Immunization Practices

ATAGI: Australian Technical Advisory Group on Immunisation

QALYs: Quality-Adjusted Life-Years

BPSU: British Paediatric Surveillance Unit

CAP: Community Acquired Pneumonia

CDC: Centre for Disease Control and Prevention

CI: Confidence Interval

CFR: Case Fatality Rate

CRM: Cross Reacting Material

HbSC: Haemoglobin SC

HbSS: Haemoglobin SS

HIV: Human immunodeficiency virus

HRQoL: Health-Related Quality of Life

IgG: Immunoglobulin

IPD: Invasive pneumococcal disease

JCVI: Joint Committee on Vaccination and Immunisation

MIC: Minimal inhibitory concentration

NIP: National Immunization programme

NVT: Non-vaccine serotype

PCV: Pneumococcal conjugate vaccine

PCV7: 7-Pneumococcal conjugate vaccine

PCV13: 13-Pneumococcal conjugate vaccine

PHE: Public Health England

PI: Principal Investigator

PM: Pneumococcal Meningitis

RCT: Randomised Control Trial

SCD: Sickle cell disease

SPn: Streptococcus Pneumoniae

ST: Serotypes

UK: United Kingdom

US: United States

VT: Vaccine type

WHO: World Health Organisation

CHAPTER 1

Introduction

1.1 Invasive and Non-invasive Pneumococcal Disease

Streptococcus pneumoniae (pneumococcus; *S. pneumoniae)* is a leading cause of morbidity and mortality in children and adults worldwide (WHO., 2007). It colonises the nasopharynx but can cause mild localised infections such as sinusitis and otitis media; rarely, the pneumococcus is responsible for occasionally more severe, invasive pneumococcal disease (IPD). The most common clinical presentations of IPD include bacteremic pneumonia, septicaemia, and meningitis. Diseases caused by pneumococcus are a major public health problem, both in terms of the large burden of non-invasive diseases such as otitis media, sinusitis and pneumonia, as well as the poor outcomes associated with more severe invasive infections including septicaemia and meningitis (Russel et al., 2011; Drijkoningen et al., 2014; ACIP., 2000; Butler et al., 1999). The magnitude of the burden caused by non-invasive cases both in the developed and developing countries is hard to define because the cause is not usually determined, including pneumococcal disease among elderly people in developing countries (WHO., 2007). In addition to the high case fatality rates, those surviving pneumococcal diseases, especially the most severe manifestation such as pneumococcal meningitis, often have significant long-term complications. In a meta-analysis including 48 studies from industrialised countries, 32% of individuals with pneumococcal meningitis had sequelae, including hearing loss, seizures, acquired brain injury and visual impairment (Jit., 2010). Also, in a recent prospective multicentre study involving 155 children in China, 30.3% had neurological complications on long-term follow up (Wang et al., 2019).

1.1.1 The Pneumococcus and Pneumococcal Serotypes

S. pneumoniae is a Gram-positive, encapsulated diplococcus *and* resides asymptomatically in the nasopharynx of healthy carriers without causing any symptoms. The organism is transmitted by direct contact with respiratory secretions from patients and healthy carriers.

Transient nasopharyngeal colonisation, not disease, is the normal outcome of exposure to pneumococci. The highest carriage rates are in young children, with reported rates of 30% to 50% (van Hoek et al., 2014). Factors associated with higher carriage rates include age <2 years, nursery attendance and out-of-home childcare, crowding, winter and parental smoking (Lexau et al., 2005). Occasionally, *S.pneumoniae* may invade locally to cause non-invasive mucosal infections such as sinusitis, otitis media and pneumonia. In susceptible individuals, particularly the immunocompromised, older adults and young children, *S. pneumoniae* infection can lead to invasive disease, including septicaemia, bacteraemic pneumonia, and meningitis, as well as other less common secondary localised infections such as septic arthritis, osteomyelitis, endocarditis and periorbital cellulitis (ACIP., 2000).

The polysaccharide capsule of *S. pneumoniae* is an essential virulence factor for invasive disease. Their unique polysaccharide capsule is used to distinguish between the different pneumococcal strains serologically. More than 97 different pneumococcal serotypes have been identified and most serotypes can cause invasive and non-invasive disease (Geno et al., 2015). These serotypes are distinguished using either the American or Danish systems. The Danish system was able to distinguish serogroups from serotypes. Most American serotypes corresponded to the Danish serotypes, except for Danish serotype 35A, which corresponded to American types 47 and 62 (Kauffmann et al., 1960). This Danish system has now been widely accepted throughout the world.

Recent acquisition of the pneumococcus is associated with IPD, although, not all pneumococcal serotypes are equally invasive; the composition and quantity of capsular polysaccharide has a major role in virulence and invasive potential. Most pneumococcal capsules are anionic and therefore negatively charged, except the capsules of serotypes 7A, 7F, 14, 33A, 33F, and 37, which are not charged (Lin et al., 2013). Serotype 1 capsule contains both a positive and a negative charge (Bentley et al., 2006), and therefore has a relatively high rate of invasion compared to its rate of colonisation (Brady et al., 2014). The less soluble nature of serotype 14 capsule compared to other serotypes makes it have a more impermeable barrier and this may explain its relatively invasive nature (Brady et al., 2014). In addition, genetic variations of this polysaccharide capsule also play a role. Currently four genes have been identified, namely *wze*, *wze*, *wzg* and *wzh* (otherwise known as *cpsA*, *cpsB*,

cpsC and *cpsD*, respectively). A detailed biochemical structure of pneumococcal capsules is beyond the scope of this thesis. However, studies suggest that the genetic make-up of the polysaccharide capsule has less of an impact on invasiveness than the capsular type (Hausdorff et al., 2000).

Apart from the pneumococcal capsule, other combinations of virulence factors have been implicated in the ability of pneumococcus to evade the host immune response and spread from the nasopharygnx to the sterile part of the body, causing pneumonia and other IPD. For example, the pneumococcal cell wall consists of peptidoglycan, the teichoic and lipoteichoic acids. These glycan chains can undergo secondary modifications, making the cell resistant to (Gisch N et al., 2015; Bui et al., 2012). The phosphorylcholine produced by the cell wall are also important for evasion of host immune responses, as well as the pili, enabling the attachment and colonization by the pneumococcus in order to evade phagocytosis (van der Poll et al., 2009).

S. pneumonia also produces an autolysin which degrades the cell wall releasing toxins such as pneumolysin which promote colonization (Jedrzejas., 2001), enhance the formation of biofilms, and reduces mucus clearance and phagocytosis (Steel HC, Cockeran R, Anderson R 2013)(Steel et al, 2013). It can also interfere with the host's immune system and has been implicated in the regulation of the complement system (Mitchell et al., 2010). In addition, the pneumococcus produces pneumococcal surface proteins which acts as adhesins to host cells and inhibit the host's immune system (van der Poll et al., 2009; Jedrzejas., 2001). Immunoglobin (Ig) A1 proteases which reduces the binding IgA's effector region of the heavy chain and obstruct the destruction of pneumococcus by these antibodies (Janoff EN et al., 2014; Chi YC et al., 2017).

Thus, while certain serotypes are infrequently isolated from the nasopharynx, they contribute disproportionately to IPD. In large studies, serotypes 1, 2, 4, 5, 7F, 8, 9,12F, 14, 16, 18C, and 19A were found to be more invasive compared to serotypes 3, 6A, 6B, 11A, 15B/C, 19, and 23F, which were generally less invasive (Kronenberg et al., 2006; Sleeman et al., 2006; Brueggemann et al., 2003; Sá-Leão et al., 2011; Rivera-Olivero et al., 2011; Yildirim et al., 2010). The primary function of the capsule in virulence is to shield the cell wall from reacting with host antibodies and complement (Kim et al.,1999). This function is likely to vary depending on the host immunity and their capacity to elicit the host antibody response. Serotypes that are poorly immunogenic in young children are often associated with virulence among children (Robbins et al.,1983). Similarly, certain serotypes are known to be less pathogenic in human. For example with serotype 27 and 11, the C-reactive protein and ficolin-2 directly binds with the capsule respectively, making them largely non-pathogenic (Brady et al., 2014; Edwards et al.,1982), suggesting that patients infected with a low

virulence serotype are likely to lack the ability to amount a protective mechanism against that serotype or have a defect in their immune system.

Population-based studies have also identified significant associations between specific pneumococcal serotypes and disease severity (e.g. death) among patients with septicaemia (Harboe et al., 2009) and pneumonia (Weinberger et al., 2010), but not meningitis. In a meta-analysis that evaluated serotype-specific pneumococci, it was found that serotypes 1, 7F, and 8 were associated with a lower odds of death, whereas serotypes 3, 6A, 6B, 9N, and 19F were associated with a higher risk of death (Weinberger et al., 2010).

Although there are significant geographical variations, with different serotypes dominating in different regions, common serotypes are consistently identified throughout the world. These variations are thought to be due to the results of age, time and possible environmental influences (Hausdorff et al., 2000). In children, prior to the routine PCV immunisation programme, the seven most common serotypes were responsible for 60-80% of all IPD in children (Robbins et al., 1983).

1.1.2 The Burden of Pneumococcal Disease

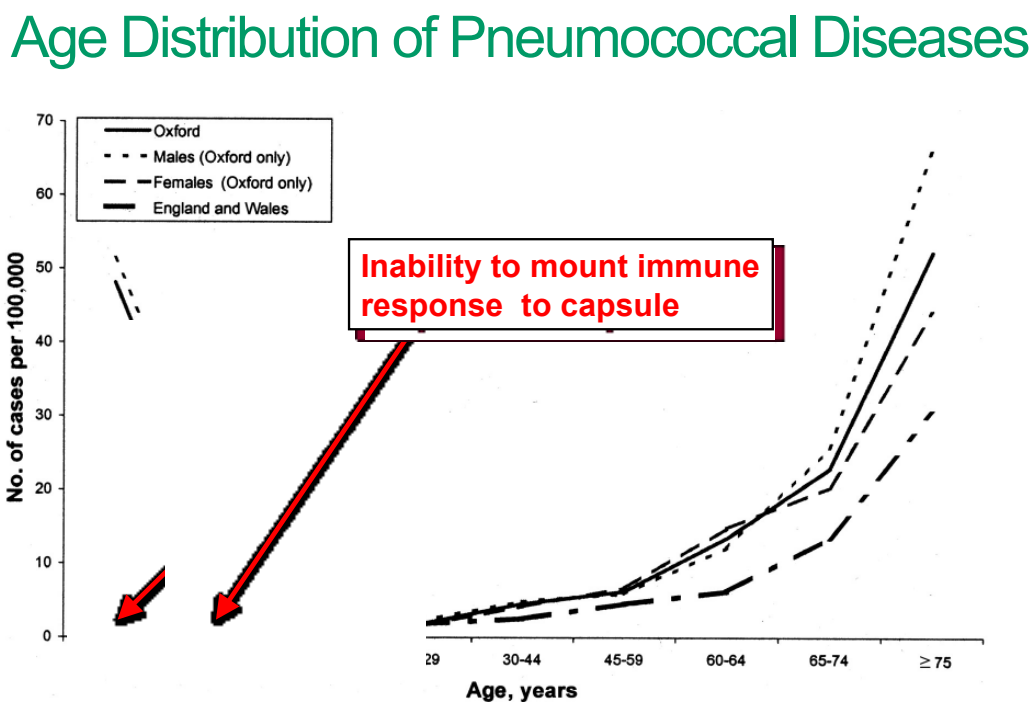
Pneumococcal disease remains a leading cause of vaccine-preventable child death and illness despite there being continuing reductions in both overall childhood mortality and pneumonia deaths. Unlike IPD where there are established surveillance systems, the overall burden of non-invasive pneumococcal disease is difficult to measure. It is estimated globally that there were 120 million episodes of non-bacteraemic pneumonia in 2010 in developing country, resulting in 1.3 million deaths in children younger than 5 years (Walker et al., 2013). Before the introduction of PCVs in low income countries, of the estimated 8.8 million global annual deaths amongst children <5 years of age in 2008, 476 000 deaths were caused by pneumococcal infections in HIV-negative children (WHO., 2008). Children and adults with underlying comorbidities have a much higher risk of serious pneumococcal disease and death (O'Brien et al., 2009). The highest burden of pneumonia deaths is in Africa and Southeast Asia, which together account for almost one million of the estimated 1.3 million pneumonia deaths worldwide in children under 5 years of age in 2011 (Walker et al., 2013), and a significant proportion of those deaths could arguably have been prevented through vaccination. However, in industrialised countries, where fatality from IPD is rare, little is

known of the characteristics children who died of IPD in the era of conjugate vaccines.

The incidence of IPD in children aged <5 years is also much higher in developing countries than industrialised countries for a number of reasons, including malnutrition, poverty, and overcrowding. Data from developing countries are generally underestimated due to inadequate facilities to establish diagnosis, self-medication and poor surveillance systems. For example, in South Africa, prior to PCV introduction, the incidence of IPD in < 2years among HIV uninfected children was 28.6/100,000, while in Gambia the incidence was estimated to be 253/100,000 in a similar age-group (Mackenzie et al., 2016). In developed countries too, the reported incidence in children <5 years old in the pre-PCV era has been variable, ranging from 17.1 to 94.7 cases/100,000 child-years, with the highest incidence in North-America and lowest in European countries (Izurieta et al., 2018).

In adults, the annual incidence of IPD ranges from 15 to 49 per 100 000 in North America, whereas from Europe, during the same period, the rates ranged from 11 to 27 per 100 000 (Kyaw et al., 2003; Reinert et al., 2005; Lynch et al., 2009). *S.pneumoniae* is the most common cause of community-acquired bacterial pneumonia (CAP) in adults. The incidence of CAP rises rapidly with increasing age, with estimated rates ranging from 18.2 per 1000 person-years in people aged 65–69 years, to 52.3 per 1000 person-years in those aged over 85 years (Jackson et al., 2004). Case fatality from CAP also increases with age, being 2.2% versus 10.3% in these two age-groups respectively, determined from studies using a large Spanish cohort (Vila-Corcoles et al., 2005). Amongst those with underlying co-morbidity, those with predisposing factors for IPD and elderly patients with severe CAP requiring mechanical ventilation case fatality rates of more than 50% have been reported (El-Solh et al., 2001). Robust data on the burden of pneumococcal disease in adults and elderly people in developing countries, especially relating to pneumonia, are lacking (Maimaiti et al., 2013). Generally, adults with underlying co-morbidities and older adults are more vulnerable to serious bacterial infection and are also less likely to develop robust immune responses to vaccination (Weycker et al., 2010). The ageing human population, especially in developed countries, poses a major challenge and will lead to a rise in the healthcare and economic burden for pneumococcal diseases worldwide. In the US, in 2004, it was estimated that the

direct healthcare costs of pneumococcal disease totalled $3.5 billion (Huang et al., 2011). A similar study in Europe estimated that the total healthcare costs for CAP could be as high as $11.7 billion annually, with one third related to indirect costs, such as loss of working days (Gibson et al., 2003). It was therefore clear, that a long lasting solution was needed to curb the burden of pneumococcal disease in developing and industrialised countries. In 2000, PCV7 was introduced in the US and later adopted in the national immunisation programme by many other countries.



Mean annual incidence of invasive pneumococcal disease, by age and sex, in England and Wales, 1995–1997, and in the Oxford region, 1995–1999.
Karen et al. J Infect Dis. 2001

1.1.3 The History of Pneumococcus

The pneumococcus was first isolated by the US Army physician George Sternberg and the French chemist Louis Pasteur in 1886 independently, following its role as a major cause of pneumonia (Sternberg., 1881; Pasteur., 1881). In 1920, due to its characteristic appearance on Gram stain, it was renamed *Diplococcus pneumoniae* (Winslow et al., 1920), which was

changed to *Streptococci pneumoniae* in 1974, since it had similar features to other bacteria in the streptococcus group. *S. pneumoniae* has played a critical role in human disease. Its capsular polysaccharide is known to be pivotal to its virulence.

However, it was not until the work of Griffith, that bacteriologist believed that hereditary information could only be transferred by descent, from one generation to another rather than horizontally, from one cell to another. Griffith worked with 2 strains of pneumococcus, rough (R) and smooth (S). The rough (R) strain was non-pathogenic and lacks capsule while the smooth (S) strain was pathogenic and has a capsule covering the cell wall. The injected R strain and killed (heated) S strain on separate mice did not cause a disease, while the injected S strain result in the death of the mice. However, when both the killed S strain and the R strain where injected together, the mice died, and only the live S strain was obtained from this dead mice, suggesting that the type R strain had been transformed into the virulent S Strain by the a 'transforming principle'. Studies of the rough and smooth colony variants of a pneumococcal strain showed that serotype-specific protective sera react with the capsule (Griffith., 1928). The chemical nature of the capsule was then elucidated to be polysaccharide (Heidelberger and Avery., 1924). Griffith experiment was therefore the first to suggest that pneumococcus are capable of transferring genetic information by transformation. This was verified by Avery and colleague, which is now known as DNA (Avery and Dubos., 1931).

These findings and work by other scientists opened the door for a number of studies in the 1930s and 1940s on vaccines aimed at preventing pneumococcal disease. In 1937, for example, Felton's capsular material was successfully used in a program of mass vaccination to abort an outbreak of pneumonia at a state hospital (Smillie., 1938).

In addition, the discovery of the antibacterial properties of the fungus-derived substance that came to be called penicillin by Fleming in 1929 completely changed the approach to treatment of pneumococcal infections (Fleming., 1929). This led to great successes in the treatment of a variety of staphylococcal and streptococcal (including pneumococcal) infections, especially those resistant to sulfonamides (Keefer et al., 1943).

However, penicillin-resistant (MIC of >0.1microgram/ml) pneumococcal strains emerged in

the 1960s and 1970s. In the 1980s, in addition to penicillin, erythromycin and trimethoprim-sulfamethoxazole continue to spread globally. Multidrug-resistant pneumococci strains were first identified in children (Jacobs et al., 1978) and were observed among isolates of serotypes 1, 14, 19F, 19A and 23F in 21 European countries in the 21st century (European Centre for Disease Prevention and Control., 2012). The mechanism by which resistance to penicillin arises in pneumococci involves decreased binding of the drug to penicillin binding proteins (PBPs), which are also known as transmembrane carboxypeptidases-enzymes involved in cell wall synthesis (Jacobs et al., 1978). Later, Hotchkiss (Hotchkiss., 1951) showed that, in addition to the genes encoding capsule production, those sequences encoding resistance to penicillin could be transferred to a previously penicillin-sensitive pneumococcus by DNA isolated from a penicillin-resistant Pneumococcus. This study opened up investigations into biochemical principles that underpin genetic transference of information. For example whole-genome sequencing is now been used in the population to study the epidemiology of capsule switching to non-vaccine serotypes following the introduction of conjugate vaccines and the emergence of drug resistance (Croucher et al., 2013). The increasing incidence of penicillin-resistant pneumococci continues globally. In the US, prior to the introduction of conjugate vaccines, 25.1% of all IPD isolates were due to penicillin-nonsusceptible strains, with serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F accounting for 80% of the resistant strains (Hofmann et al., 1995; Kyaw et al., 2006). Similar observation was made in the UK with a 2.5% rise in penicillin resistance between 1990 and 1995 (Goldsmith et al., 1997). In the UK, however, the proportion of dual resistance has remained low post PCV between 2%-4% for erythromycin, tetracycline and penicillin, with only 2% resistant to all three antibiotics (Health Protection Report., 2016). Data from 38 countries looking at antibacterial resistance over time using their genetic constituents and other methods showed that almost 40% of pneumococci display multidrug –resistant phenotypes (Farrell et al., 2008). However, the introduction of conjugate vaccines has changed the epidemiology of these resistant strains with significant reduction in resistant strains albeit with serotype replacement. Newer antibiotics, as well as different preventive and therapeutic strategies, are therefore needed to combat this trend.

1.1.4 Risk Factors for Pneumococcal Disease

Certain groups of people are at higher risk of IPD (Salisbury et al., 2006). In the USA, prior to the introduction of PCV7, African American, Alaska Natives, and some American Indian populations had increased risk of IPD compared to Caucasian populations. The extent to which increased risks are attributable to factors other than race and ethnicity are not clear. The increased risks of race persist despite controlling for income (Singleton et al., 2007). In one study, IPD was more common in blacks than in whites (CDC., 2013).

In addition, a number of case control studies have also demonstrated a strong association of IPDs with the presence of underlying disease, environmental factors, larger family size, and with attendance at out-of-home childcare in the preceding 3 months, suggesting that factors other than ethnicity also contribute to a higher infection risk (Nuorti et al., 2010). Children with sickle cell disease (SCD) or with human immunodeficiency virus (HIV) infections, especially 2 year-olds, have a markedly higher incidence of IPD, as do those with asplenia, nephrotic syndrome, immunodeficiency, immunosuppressive therapy and conditions associated with cerebrospinal fluid leak. Children with a cochlear implant, in particular those who received an implant with positioner, also have been shown to be at increased risk of pneumococcal meningitis (van Hoek et al., 2012).

In a study assessing the risk of IPD in HIV infected children, a 9- to 43-fold increased relative risk of IPD was observed (Bliss et al., 2008). Even with the routine use of highly active retroviral therapy (HAART), the incidence of IPD was only reduced by 50% in HIV-infected children compared to age matched, HIV uninfected children (Nunes et al., 2011).

1.1.5 Pneumococcus-influenza virus co-infections

Evidence suggests that many pathogens interact. A pathogen can affect the severity susceptibility and infectivity of another pathogen. This is particularly true for *S. pneumoniae* and viruses, which are considered as a primary risk of IPD. This role of viruses particularly Influenza A in facilitating the progression of *S. pneumoniae* infection was clearly demonstrated in the 20th century pandemics (Morens et al., 2008; Brundage et al., 2008;

Chien et al., 2009). This was corroborated in the recent trend of the 2009 H1N1 pandemic, where there was 17,000 fatalities reported by WHO, of which majority were due to co-infection with *S. pneumonia*. Epidemiological and clinical evidence also suggests that an increased incidence of pneumococcal disease occurs during non-pandemic periods, characterised by peaks during the winter months (Dowell et al., 2003).

However, the mechanism by which Influenza A increases the incidence of IPD remains unclear. One of the first proposed mechanisms is the destruction of the respiratory epithelium by Influenza A, enhancing the adherence of pneumococcus to the exposed basement membranes (Harford and Hara., 1950; Harford et al., 1949). Other recent mechanisms have been suggested to include, Influenza A induced neutrophil dysfunction, with excessive influx into the lungs, resulting in lung damage and increase mortality(Karlström et al., 2011), increased bacterial adherence due to virus-induced changes in adherence receptors and alterations in innate signalling and other cellular responses (McCullers., 2006). Others have also postulated that the production of interferon-y (IFN-y) by activated T cells which result in decreased in binding and phagocytosis by macrophages of *S. pneumoniae* (Ludewick et al., 2011), while the role of dendritic and natural killer cells remains unclear (Olliver et al., 2011). In contrast, in one study involving 796 nasopharyngeal aspirates from hospitalised patients with any respiratory viruses using real-time multiplex PCR, 50% were colonize with *S. pneumoniae*, and codetection was associated with reduced severity of viral LRTI (Jung et al., 2020). However, despite reasonable amount of work on the effect of Influenza A on *S. pneumoniae*, there is a paucity of research regarding the effect of the pneumococcus on viral infection.

1.2 Pneumococcal Vaccines

1.2.1 Pneumococcal Conjugate Vaccines

There are currently two types of pneumococcal vaccines licensed, the plain polysaccharide vaccine and the polysaccharide-conjugate vaccine. The first plain polysaccharide pneumococcal vaccine contained purified capsular polysaccharide antigen from 14 different pneumococcal serotypes. In 1983, a 23-valent polysaccharide (PPV23) was licensed in the

US, and included 11 additional serotypes to PCV13, including 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F. The plain polysaccharide vaccines were poorly immunogenic; the polysaccharide antigens were not processed by antigen-presenting cells (APC) but interacted directly with B cells to induce antibodies in the absence of T-cells (i.e. thymic independent). Such T cell-independent responses were restricted in a number of ways. Most importantly, they failed to induce significant and sustained antibody concentrations in young children below the age of 18 months, who had the highest risk of IPD (Kelly et al., 2005; Baker 1992; Käyhty et al., 1984).

In order to overcome this problem, protein-polysaccharide conjugate vaccines were developed. The conjugation of pneumococcal polysaccharide to carrier proteins elicits a T-cell dependent immune response, which is characterised by the differentiation of memory B cells and much higher antibody concentrations, resulting in (i) the induction of immunological memory, (ii) antibody class switching and (iii) avidity maturation of the resulting antibodies.

There are three different polysaccharide-conjugate vaccines, although PCV7 has now been replaced with PCV13:

- The 7-valent pneumococcal conjugate vaccine (PCV7) contains polysaccharide from seven common capsular types (PCV7). These polysaccharides are conjugated to diphtheria cross-reacting material (CRM197).
- The 10-valent PCV (PCV10) includes 3 extra serotypes: 1, 5, and 7F
- 13-valent pneumococcal conjugate vaccine (PCV13) contains three more serotypes in addition to PCV10: 3, 6A, and 19A.

All the pneumococcal vaccines are inactivated and, since they do not contain live organisms, they cannot cause disease in the host. In the US, PCV7 was licensed and introduced into the national immunisation programme (NIP) in 2000 with a catch-up for children up to 2 years of age. In Australia, it was introduced in 2002 and was initially recommended for high-risk children, but in 2005 PCV7 was included in the NIP for all children. In Europe, PCV7 was licensed in 2001 and introduced into the national immunization programs (NIPs) as a universal childhood vaccine around 2006–2008. Its introduction into the NIPs in different

countries varied, with some countries initially only recommending vaccination for high-risk children before generalising administration to all children (e.g., UK, Germany, and France).

1.2.2 Pneumococcal Polysaccharide Vaccines

The 23-valent pneumococcal polysaccharide vaccine (PPV23) protects against 16 more serotypes compared to PCV7 and, in many countries, has been recommend for at-risk persons aged 2 years and above and the elderly. Studies have shown some short-term effectiveness against both invasive (Andrews et al., 2012) and non-invasive (Ansaldi et al., 2005; Kim et al., 2019) disease caused by the vaccine serotypes but its use in at-risk individuals and in the elderly has been controversial (Vadlamudi et al., 2019). With poor vaccine uptake compared to the childhood programmes and little or no overall impact observed on disease incidence, it has been suggested that future PCVs should include these additional PPV23 serotypes, which are now the main cause of IPD in countries with established immunisation programmes with the current higher-valent PCVs.

1.2.3 Impact of Pneumococcal Vaccination on Invasive Pneumococcal Disease

Following the introduction of PCV7 into national childhood immunisation programmes, most countries have reported a significant decline in IPD caused by PCV7 serotypes, not only in the vaccinated cohorts but also in older unvaccinated cohorts because of indirect (herd) protection (Davis et al., 2013). Widespread availability of PCVs also reduced the number of deaths due to IPD in children under 5 years of age, from over 800,000 annual deaths before PCV introduction to 541,000 deaths in 2008 (O'Brien et al et al., 2009; WHO., 2008).

Significant reductions in carriage of PCV7 serotypes in vaccinated young children has demonstrated that nasopharyngeal carriage in infants and toddlers was an important driver of pneumococcal transmission in the household and wider community (Hennessy et al., 2005). Similar conclusions were drawn in a systematic review assessing nasopharyngeal carriage in children after the introduction of pneumococcal conjugate vaccination (Cohen et al., 2011). However, the overall carriage rate in children have remained unchanged because PCV7 serotypes were replaced with non-PCV7 serotypes in carriage and, consequently, in disease

(Conklin et al., 2014). Despite the increase in serotype replacement disease due to non-PCV7 serotypes, overall IPD rates, especially in developed countries with high vaccine uptake, have declined significantly in across all age groups and especially in the vaccinated cohort (Kaplan et al., 2013). In the UK, an overall reduction of 37% compared to the pre-PCV7 period was observed across all age-groups through a combination of direct and indirect (herd) protection (Waight et al., 2015).

Other countries that introduced PCV7 also observed similar rapid reductions in overall and PCV7-serotype IPD, with variable extent of replacement disease (Gilmour et al., 2008; Kellner et al., 2005; Zangeneh et al., 2011; WHO et al., 2007). In the review published by Myint et al, on the impact of PCV7 on IPD in Europe, vaccine-type IPD reduction ranged from 39.9% in Spain to 99.1% in the United States with a median rate reduction of 90.1% (Myint et al., 2013). Other countries also observed replacement with non-vaccine serotypes, in both carriage and disease, following the successful implementation of PCV7 (Miller et al., 2011; Weinberger et al., 2011; Singleton et al., 2007; Park et al., 2010). The impact of PCVs on pneumococcal meningitis in countries with established pneumococcal immunisation programmes has been variable, with some countries reporting significant reductions after PCV7 introduction and others reporting no change, or a decline only after PCV13 introduction (Ben-Shimol et al., 2017; Alari et al., 2016; Hsu et al., 2009; Ruiz-Contreras et al., 2017; Tsai et al., 2008; Liset et al., 2015).

The main replacing serotypes varied in different countries but some of the emerging serotypes were consistently common, including serotypes 6C, 19A, 22F, 15 and 33 (Jacobs 2008; Park et al., 2008; Pelton et al., 2007). Replacement disease with serotype 19A was a particular problem in many parts of the world, but especially in the US, because this serotype was associated with resistance to multiple antibiotics (Pai et al., 2005; Yildirim et al., 2012). Since PCV7 licensure, two higher-valent vaccines (PCV10 and PCV13) were licensed after they were shown to elicit an adequate immune response against all the vaccine serotypes with demonstrable non-inferiority against the serotypes they have in common with PCV7 (Vanderkooi et al., 2012).The effectiveness of these vaccines was described with a 0.92% vaccine failure rate per 100,000 person years over 8 years surveillance (in a 10 birth cohort) in England and Wales and 2% rate in a systematic review of the literature (Oligbu et al., 2017a; Oligbu et al., 2016).

Globally, the introduction of higher-valent PCVs, including those countries with established PCV programmes, has led to additional reductions in overall IPD rates, albeit with some serotype replacement in carriage and disease with new emerging serotypes. Currently, the 10 most common serotypes causing IPD in Europe include (in order of frequency) 8, 3, 22F, 12F, 19A, 9N, 7F, 15A, 33F, 10A, accounting for 62% of typed isolates. Of the cases in children under 5 years of age, 72% were caused by a serotype not included in any PCV. Among cases aged 65 years and over, 71% were caused by a PPV23 serotype, and 32% were caused by a PCV13 serotype especially in the elderly (European Centre for Disease Prevention and Control., 2017).

1.2.4 Impact of Pneumococcal Vaccines on Pneumonia

Prior to PCV introduction, a randomised controlled trial (RCT) conducted in the Gambia using a 9-valent PCV (PCV9) in the early 2000s found that the vaccine reduced all-cause mortality by 16% (3-28%) (Miller et al., 2011). Following this trial, the WHO recommended that global use of PCVs would reduce mortality due to pneumonia in children by 25-30% (World Health Organization., 2013). Subsequently, a recent global burden assessment found that about half of all fatal lower respiratory tract infections (LRTIs) were caused by pneumococcus and a significant proportion of these were, thus, potentially vaccine-preventable (Troeger et al., 2017). However, a systematic review and meta-analysis of randomized controlled studies did not find PCVs to have a statistically significant effect on death due to pneumonia (Lucero et al., 2009; Ewald et al., 2016). This may be due to a number of reasons, one being that the magnitude of serotype replacement in pneumococcal pneumonia is not known and is difficult to measure because of diagnostic, methodological and surveillance challenges. In particular, it is difficult to disentangle the contribution of vaccine-related changes to natural fluctuations in serotype dynamics in different populations.

1.2.5 PCV Impact on Antibiotic Resistance

The impact of PCVs on antibiotic resistance among pneumococcal strains causing IPD has varied in different part of the world. In 1998, prior to PCV use, the Centre for Disease Control and Prevention reported that 24% of strains associated with IPD were non-

susceptible to penicillin and that serotypes 6B, 9V, 14, 19F, and 23F accounted for 78% of penicillin non-susceptible strains (Whitney et al., 2000). Four years after the introduction of PCV7 in the US, the rate of IPD caused by penicillin non-susceptible strain decrease from 6.3 to 2.7 cases per 100,000 and that due to multidrug-nonsusceptible strains also decrease from 4.1 to 1.7 cases per 100,000 (Kyaw et al., 2006). During the PCV7 era, serotypes 7F and 19A, among others, emerged mainly through clonal expansion as the most common replacing serotypes causing meningitis in Europe and the USA (Waight et al., 2015; Richter et al., 2013; Hanquet et al., 2010). However, unlike the UK, the emerging serotype 19A strains exhibited high rates of resistance to multiple antibiotics in several countries, including France and the USA (Janoir et al., 2016; Mahjoub-Messai et al., 2009). In South Africa, two years after PCV7 introduction, vaccine effectiveness against all-serotype multidrug-resistant IPD was 96% (95% CI, 62%, 100%) among HIV-uninfected children (Cohen et al., 2014). Following three years of PCV use, penicillin non-susceptible IPD rates declined by 47% (95% CI: 38%, 55%) in South African children <2 years; this was predominantly due to a decline in the proportion of penicillin non-susceptible PCV7 serotypes from 70% of isolates in 2009 to 47% of isolates in 2012 (Von Gottberg et al., 2014).

Following the introduction of PCV13, many countries have demonstrated significantly large reductions in IPD caused by the additional PCV13 serotypes, including serotype 19A and the antimicrobial resistant clones (Moore et al., 2016; Isturiz et al., 2017; Gaviria-Agudelo et al., 2016; Sader et al., 2019). However, this serotype continues to circulate and cause invasive disease, despite widespread use of PCV13 in industrialised countries with established immunisation programs (Balsells et al., 2017).

1.3 PHE Surveillance network

In 1996, a dataset of all IPD reported in England and Wales was created, by linking computerised laboratory reports given to Public Heath England (PHE) formerly the Health Protection Agency (HPA). This dataset consists of cases in which *S. pneumoniae* has been identified by culture, or more rarely by antigen detection or PCR, in a normally sterile site. The isolates are also transferred to PHE Respiratory and Vaccine Preventable Bacteria

Reference Unit (RVPBRU) formerly Respiratory and Systemic Infection Laboratory, for serotyping (Trotter et al., 2010). In the UK, blood cultures and cerebrospinal fluid samples are routinely obtained from patients who require admission to the hospital. Repeat samples from sterile sites within 30 days from the same individual were regarded as part of the same episode. Antimicrobial susceptibility testing was done according to British Society for Antimicrobial Chemotherapy guidelines (Andrews., 2009), and results are available for penicillin and erythromycin, together with some clinical information such as whether a patient had meningitis. PCR diagnosis became available in PHE on cerebrospinal and pleural fluid samples from patients with suspected meningitis or empyema since January 2006, with serotyping done with a pneumococcal polysaccharide antigen assay (Sheppard et al., 2011).

After the introduction of PCV7 vaccination in September 2006, all patients with IPD in the vaccine-eligible cohorts or catch-up group were followed up actively for vaccination history and information on clinical presentation, improving case ascertainment of IPD. However, this is still nowhere near the active surveillance implemented by the ABCs in the US. It is important to emphasise that the enhanced surveillance was only limited to vaccine eligible cohort (i.e. under 2 year-olds) and only extended until they turned 5. This age group constituted only a very small proportion (<5%) of all the meningitis cases annually and, therefore, contributed to a very small number of additional cases of "clinically diagnosed meningitis with positive blood cultures". Excluding these cases had no significant impact on the reported trends.

Before 2010, reporting was voluntary; consequently, there was also an increasing trend in ascertainment of cases during the period, as evidenced by a parallel increase in cases of other invasive bacterial infections reported to PHE, which continued up until 2009–10 (Flasche et al., 2011).

To correct for this increase, the average percentage annual change in total invasive pneumococcal infections from 2000–2006 was calculated for each age group, and this was then used to retrospectively increase counts to the projected 2009–2010 level of ascertainment, when the increase then stabilise. For example, pre-PCV7 invasive pneumococcal disease reports in children younger than 2 years increased by 1·67% annually;

thus, for 2005/06, an inflation factor of $1{\cdot}0167^4=1{\cdot}07$ was applied to the raw numbers for that year (Miller et al., 2011).

Serotypes 6A and 6C were routinely distinguished from each other from May, 2009, onwards, and have therefore been combined in this analysis. Full serotyping within serogroups in the PHE reference laboratory started in 2000 (Miller et al., 2011). The proportion of total isolates serotyped improved over time, from 50% in 2000/01, to 79% in 2005/2006, to 90% in 2009/2010, and remained between 91% and 97% in subsequent years with variation between age groups. In the same period, the proportion of cases with missing age data decreased from 4·4% to 0·1% and the population size increased in most age groups (Office for National Statistics., 2011). To correct for these changes, the raw number of yearly invasive pneumococcal infections with known age and serotype data were adjusted with the assumption that cases with missing age (<1% of cases) and serotype information had the same age and serotype distribution as those cases in which this information was known, The number of extra cases were then added to the raw numbers in each category. Numbers were then further adjusted to 2009–2010 Office for National Statistics population denominators in each age group (Office for National Statistics., 2011). Cases prevented were estimated as the difference between the expected number of cases by age group, through the use of the corrected trends in the absence of vaccination and the observed number of cases after the introduction of each vaccine.

Public Health England has legal permission, provided by Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002, to process patient confidential information for national surveillance of communicable diseases (http:// www.legislation.gov.uk/uksi/2002/1438/regulation/3/ made) and includes Public Health England's responsibility to monitor the safety and effectiveness of vaccines.

The “clinical diagnosis” of meningitis requires a positive pneumococcal culture from a sterile site, typically the blood. It is acknowledge that pneumococcal meningitis cases with a positive blood but not CSF culture may be missed if they are not reported as “meningitis”. This will underestimate the total burden of pneumococcal meningitis, but should not affect the trends over time or the vaccine impact analysis in this thesis.

In addition, there is the issue of unconfirmed bacterial meningitis where the pathogen may not be identified due to diagnostic practices, but there was no evidence of any change in diagnostic practices over the surveillance period in this thesis. Indeed, since pneumococcal meningitis is such an important diagnosis with significant case fatality as well as long-term morbidity, the experience is that any under-reporting is likely to be minimal. In addition, the pneumococcus is likely to contribute to a proportion of such cases across all age groups. Since such cases will not be picked up in the national pneumococcal surveillance, and therefore, the true incidence of pneumococcal meningitis is likely to be higher than that reported in the surveillance and thesis. However, even if the overall incidence was lower, the trends observed over time – and therefore the impact of PCVs will remain.

Because of these surveillance factors outlined above, included in this thesis is a pre-PCV adjustment to make the pre-vaccine epidemiology comparable to the post-vaccine epidemiology. This has involved imputation of missing data and a pre-vaccine trends adjustment. Since the data had been corrected for any under-ascertainment in the pre-PCV7 period, this should help nullify any surveillance artefacts in this analysis. This surveillance is sufficiently sensitive to observe large reductions in vaccine-type meningitis cases after the introduction of both PCV7 and PCV13.

The study period in this thesis thus spanned 16 years, 6 years of baseline before PCV7 vaccination from 2000–01 to 2005–06, 4 years after PCV7 vaccination, from 2006–07 to 2009–10, and 6 years after PCV13 introduction, from 2010–11 to 20015–16. Study years run from July to June.

1.4 Aims and Objectives

The aim of this thesis was to provide novel contribution to knowledge with regards to assessing the impact of pneumococcal conjugate vaccines on IPD following the replacement of PCV7 with PCV13 in the UK childhood immunisation programme. This thesis focused particularly on childhood IPD, with emphasis on severe manifestations of IPD and understanding the disease in high-risk populations.

The specific objectives of the thesis were to:

1. Undertake a systematic review of the literature to describe the risk, characteristics and outcomes of children with PCV failure (i.e. development of vaccine-type IPD in a child who was appropriately immunised with PCV for age) [Chapter 3] (Oligbu et al., 2016)
2. Elucidate national surveillance data, to estimate the incidence, clinical characteristics and outcomes of IPD in children with PCV failure in England and Wales since the introduction of the PCV7 programme in 2006 [Chapter 4] (Oligbu et al., 2017a)
3. Undertake a systematic review of the literature to describe the risk, characteristics and outcomes of IPD in children with sickle cell disease during the era of pneumococcal conjugate vaccination [Chapter 5] (Oligbu et al. , 2019a)
4. Use multiple national sources, to describe the risk, clinical characteristics and outcomes of IPD in a cohort of children who were identified with sickle cell disease through a national neonatal screening programme and who would have been eligible for PCV13 [Chapter 6] (Oligbu G et al., 2018)
5. Evaluate national surveillance data to estimate the impact of PCV7 and PCV13 on the pneumococcal meningitis in England and Wales [chapter 7] (Oligbu et al., 2019b)
6. Describe a detailed clinical case follow-up of all children suspected to have died of IPD in England and Wales since the introduction of PCV7 in 2006 [Chapter 8] (Oligbu, et al. 2017b)

CHAPTER 2

Pneumococcal conjugate vaccine failure in children: A systematic review of the literature

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CHAPTER 3

Characteristics and Serotype Distribution of Childhood Cases of Invasive Pneumococcal Disease Following Pneumococcal Conjugate Vaccination in England and Wales, 2006–2014

Godwin Oligbu, Sarah Collins, Nick Andrews, Carmen L. Sheppard, Norman K. Fry, Mary P. E. Slack, Ray Borrow, and Shamez N. Ladhani

Clin Infect Dis. 2017 Oct 1;65(7):1191-1198

https://www.ncbi.nlm.nih.gov/pubmed/29309553

CHAPTER 4

Risk of invasive pneumococcal disease in children with sickle cell disease in the era of conjugate vaccines: a systematic review of the literature.

Godwin Oligbu, Mohammad Fallaha, Leon Pay, Shamez Ladhani

British Journal of Haematology. 2019 May;185(4):743-751

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CHAPTER 5

Risk of Invasive Pneumococcal Disease in Children with Sickle Cell Disease in England: A National Observational Cohort Study, 2010–2015

Godwin Oligbu, Sarah Collins, Carmen Sheppard, Norman Fry, Moira Dick, Allison Streetly, Shamez Ladhani

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CHAPTER 6

Effect of Pneumococcal Conjugate Vaccines on Pneumococcal Meningitis in England and Wales, July 1, 2000-June 30, 2016

Godwin Oligbu, Sarah Collins, Abdelmajid Djennad, Carmen L. Sheppard, Norman K. Fry, Nick J Andrews, Ray Borrow, Mary E Ramsay, Shamez Ladhani.

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CHAPTER 7

Childhood Deaths Attributable to Invasive Pneumococcal Disease in England and Wales, 2006–2014

Godwin Oligbu, Sarah Collins, Carmen L. Sheppard, Norman K. Fry, Mary Slack, Ray Borrow, and Shamez N. Ladhani

Clin Infect Dis. 2017 Jul 15;65(2):308-314

https://www.ncbi.nlm.nih.gov/pubmed/28605414

CHAPTER 8

Discussion

9.1 **Pneumococcal Vaccine Failure**

The published articles assessed the impact of pneumococcal conjugate vaccines (PCVs) on invasive pneumococcal disease (IPD) especially in children and those with underlying comorbidities, particularly children with sickle cell disease (SCD). In the UK, PCV7 and PCV13 were introduced into the national immunisation programme in 2006 and 2010 respectively, but at variable times in other industrialised countries. These vaccines are highly effective in preventing IPD caused by the respective vaccine serotypes (Waight et al., 2015). However, the overall reduction was offset by increase in IPD cases due to non-vaccine serotypes. Whilst much has been published about PCV7 and its impact on IPD, there was a paucity of similar information for PCV13. This thesis provides a new insight into PCV13 and it's impact on IPD.

Whilst PHE national surveillance monitored disease rates across all age groups in England, there were a number of important questions that remained unanswered following PCV13 implementation. The first part of the study (chapters 3 and 4) aimed to describe the characteristics of children with PCV failure, initially through a systematic review of the literature, followed by analysis of national surveillance data.

In chapter 3, a systematic review of all observational studies reporting PCV failures cases was performed. This was the systematic review of children with PCV failure. A total of 159 vaccine failure cases were identified, representing 2.1% of the reported IPD cases from 20 publications in children aged <5 years. The rate of PCV failure was low, with PCV failure cases accounting for only 2% of total IPD cases, irrespective of the vaccine (PCV7, PCV10 or PCV13) or schedule (2+1, 3+0, 3+1) used in industrialised countries. The review also found a high co-morbidity prevalence but a low case fatality rate, which was more likely to be associated with underlying comorbidity (Oligbu et al., 2016). Comorbidity prevalence in the published literature, relating almost exclusively to PCV7 failures, ranged between 10%

and 36%, which was in keeping with the prevalence in UK children with IPD (Ladhani et al., 2013), with immunosuppression, mainly malignancy, and cardiac conditions predominating. These are known risk factors for IPD, irrespective of vaccination status and, therefore, it was not surprising that such children were also at increased risk of vaccine failure.

The use of national surveillance data in England and Wales was the largest cohort study assessing vaccine failure cases from the inception of routine PCV in 2006 over an 8-year surveillance period in England and Wales. It was also the first published article comparing PCV13 with PCV7 vaccine failure cases. In this study, only161 children (<1/100,000 vaccinated person-years) had PCV failure among 10 birth cohorts (around 700,000 babies per birth cohort) over the 8-year surveillance period (Oligbu et al., 2017a). The study confirmed that PCV failure was very rare, even when compared with *Haemophilus influenzae* type b (Hib) conjugate vaccine, with a reported vaccine failure rate of 2.2/100000 UK children over a 6 year and 5 month period (Heath et al., 2000), and for the meningococcal group C (MenC) conjugate vaccine, where 53 vaccine failure cases were identified among <18-year-olds during the first 4 years after vaccine introduction (Auckland et al., 2006). Unlike MenC vaccine failure cases where the children were previously healthy, but similar to Hib vaccine failures, the presence of underlying comorbidities and waning antibodies after vaccination were the potential explanations for vaccine failure among children receiving PCV (Heath et al., 2000; Auckland et al., 2006).

Compared to serotypes causing IPD in the pre-PCV7 period, serotypes 6B and 19F were over-represented among vaccine failure cases. These two serotypes had the lower antibody responses after infant immunisation (Goldblatt et al., 2010) and the lowest serotype-specific vaccine effectiveness after PCV7 introduction (49% and 70%, respectively) (Andrews et al., 2011). Others have also reported a predominance of these two serotypes among PCV7 failure cases (Park et al., 2010), which were responsible for more than half of the PCV7 failures in our cohort.

After PCV13 introduction, serotype 3 and 19A were over-represented among vaccine failures. Low vaccine effectiveness for these serotypes has been reported in England and Wales (Andrews et al., 2014). In infants, serotype 3 elicited the lowest post-primary and post-

booster antibody responses of the additional PCV13 serotypes (Snape et al., 2010). For this serotype, it is estimated that very higher serum immunoglobulin G (IgG) concentrations (>2.83 µg/mL) were required for protection against the disease compared to the internationally accepted threshold of 0.35 µg/mL (Andrews et al., 2014); such high concentrations were rarely attained after vaccination (Snape et al., 2010).

Unlike other serotypes, the clustering of serotype 19A vaccine failure cases around 12 months of age may indicate waning immunity after the 2 infant priming doses. It is possible that a 3-dose priming schedule before the first birthday might reduce vaccine failure rates by inducing higher post–primary immunisation antibody concentrations before the 12-month booster, but this would require additional doses and cost. However, the low prevalence of PCV7 failures after PCV13 introduction was reassuring and it is likely that PCV13 failures will also decline in the coming years as vaccine serotypes stop circulating in highly immunised populations such as the UK (Oligbu et al., 2017a). Given that almost a quarter of PCV failure cases had underlying risk factor for IPD, the extent of immunological investigations for individual children with PCV failure is likely to require careful clinical assessment, taking into account the family and past history of serious infections as well as the severity of IPD (Oligbu et al., 2017a). An underlying immune deficiency is more likely in children who develop IPD after 2 years of age (Gaschignard et al., 2014), and those with recurrent IPD (Ingels et al., 2015), but has not been reported for children with PCV failure, possibly because this is such a rare event and there was no robust evidence base to recommend routine investigations and management of children with PCV failure. Further, this work reported that vaccine failure rates were higher after 2 PCV doses in infancy and lowest after completion of the recommended 3-dose schedule, most likely because of a combination of factors, including higher vaccine effectiveness after 3 doses, lower IPD incidence in older ages, and more time for herd protection effects after PCV introduction (Oligbu et al., 2017a). Interestingly, it was also observed that children with PCV13 failures were more likely to be healthy and develop LRTI, a less severe form of IPD, whereas those with PCV7 failures were more likely to have comorbidities and develop septicaemia (Oligbu, et al., 2017a). In agreement with this observation, in a study in Portugal, of the 22 children who were appropriately vaccinated with PCV13, 19 children developed complicated pneumonia, of which serotype 3 predominated (Silva-Costa et al., 2018). Similar findings

were reported in Barcelona, among the 84 children with IPD, 9 children had PCV13 failure. The majority of which were due to pneumonia and serotype 3 was isolated in two-third of the cases (Moraga-Llop et al., 2016).

Taking the findings of the studies presented in chapters 3 and 4, it was reassuring to note very low rates of recurrent IPD and deaths among vaccine failure cases, and most cases had an identifiable risk factor, such as asplenia, immunosuppression or cochlear implant (Ladhani et al., 2013; Alsina et al., 2015; Ingels et al., 2014; Sanz et al., 2014; Mason Jr et al., 2007). On the other hand, children with recurrent IPD and no obvious risk factors were more likely to have an underlying immune deficiency, irrespective of their previous pneumococcal vaccination status (Ingels et al., 2015; Gaschignard et al., 2014). Such children, therefore, should be subjected to a thorough immunological assessment and investigation as detailed in the publication.
Chapter 3, in particular, demonstrated the potential strengths of combining outcomes of rare events through a systematic review of the literature. However, the lack of detailed information on vaccine failure cases in the review was a significant limitation; It is also important that future studies report vaccine failure rates using the total number of vaccinated children and their at-risk time period so that different vaccines, immunisation schedules and populations can be compared. This work also identified a clear need to establish both international and national registers for rare outcomes such as vaccine failure, as part of post-vaccine implementation surveillance in countries with established immunisation programmes to allow meaningful analysis of the data collected, and to monitor trends over time.

9.2 **IPD and Sickle Cell Disease**

Patients with sickle cell disease (SCD), especially young children, are known to have a very high risk of IPD and pneumococcal vaccination is recommended to reduce this risk, along with daily penicillin prophylaxis for children less than 5 years of age. The work presented in Chapter 5 aimed to systematically review the published literature on the impact of PCVs in children with SCD from 2000 to 2017. A total of 9,438 participants aged up to 22 years with SCD were included in the final analysis and 182 developed IPD. This identified a very low

rate of IPD of 1.9% in children with SCD, many of whom also had other associated comorbidities (Oligbu et al., 2019a).The overall CFR in the published studies was 11.5%, which, although lower than the 15% reported in industrialised countries prior to PCV introduction (Adamkiewicz et al., 2003; Hord et al., 2004; Gaston et al., 1986), remains unacceptably high.

Within the published literature, a few studies had reported a lower IPD rates in children with SCD during PCV7 compared with PPV23 (Halasa et al., 2007; Payne et al., 2013). In the US, in comparison to the pre-PCV period, the rate of IPD decreased by 93.4% (from 2044 to 134 cases per 100,000 person-years) (Halasa et al., 2007), and comparing with healthy less than 18 years old, African-American, there was 53% vs 74% decline (Payne et al., 2013). However, the impact of PCV13 had not been well established.

National surveillance data for England were therefore linked to study the impact of PCV13 on IPD in children with SCD. Despite an overall decline in IPD incidence, children with SCD were still 49 times more likely to develop IPD and 5 times more likely to die of their infection compared to their healthy peers (Oligbu et al., 2018a). However, this increased risk was substantially lower than the >600 fold increased risk reported in the absence of preventive strategies (Overturf et al., 1977). Nearly all IPD episodes in children with SCD occurred on or before their 2nd birthday, which is not surprising because this age-group struggles to mount protective antibodies against the polysaccharide capsule of encapsulated bacteria such as the pneumococcus.

The study also found that most IPD cases were due to serotypes not covered by PCV13, particularly serogroup 15. Others countries with established pneumococcal vaccination also reported a disproportionate proportion of IPD cases due to non-PCV serotypes in children with SCD compared with children without SCD after PCV introduction (Payne et al., 2013; Halasa et al., 2007; Martin et al., 2018; Navalkele et al., 2017). Although, there were no cases of meningitis in our SCD cohort, the CFR of 27% in children with homozygous SCD (HbSS) was much higher than that reported for overall childhood IPD (4.4%), IPD in children with comorbidities (9.1%) and even pneumococcal meningitis (11.0%) in England and Wales (Ladhani et al., 2013). However, two of the three IPD-related deaths in this study occurred in

prematurely-born infants, who are also at increased risk of IPD and fatal outcomes (Shinefield et al., 2002).

The lack of penicillin resistance among pneumococcal isolates causing IPD in our cohort of children with SCD may suggest that these children were not adherent to penicillin prophylaxis at the time of infection. Nationally, surveillance of children with SCD found that 97% of children with SCD were prescribed penicillin prophylaxis by 6 months, with only seven refusals during the follow-up period of this study (Streetly et al., 2018). A recent systematic review found that compliance rates for long-term medications in children with SCD ranged from 16% to 89% (Duncan et al., 2016). Given that most cases of IPD in SCD are no longer vaccine preventable, Healthcare professionals need to work more closely with families with SCD to emphasise the importance of penicillin prophylaxis, facilitate rapid access to healthcare facilities, allay misguided beliefs and explore any barriers (Oligbu et al., 2018a). This study also highlighted the need for higher valency PCV or, preferably, a universal vaccine targeting all pneumococci irrespective of their capsular serotype (Ladhani et al., 2015).

A consistent finding within the two publications presented in chapter 5 and chapter 6 was that after PCV7 introduction and subsequent replacement with PCV13, serogroup 15 appeared to be particularly common cause of IPD among children with SCD, accounting for half of IPD cases. Genomic analysis of invasive isolates and murine SCD studies have suggested that some pneumococcal strains may be particularly adapted to cause invasive disease in children with SCD (Carter et al., 2014). In a recent review of S. pneumonia isolated in England and Wales from multiple sources, serotype 15A has increased in all areas compared to pre-conjugate vaccine era and also showing triple resistance to penicillin, macrolides and tetracyclines. In addition, most of these multidrug-resistant 15A isolates were sequence type (ST) 63 variants, whereas susceptible 15A isolates were clonally diverse (Sheppard et al., 2016). However, the virulence and aggressiveness of this serogroup compared to other more prevalent serotypes is not known and additional studies beyond the scope of this thesis are needed to better understand this observed association.

In many industralised countries, PPV23 is recommended for at-risk children from 2 years of age, including SCD. This vaccine aims to protect against 11 additional serotypes, including 15B, which is now the commonest cause of IPD in patients with SCD. Unlike PCVs, however, PPV23 is a polysaccharide vaccine and therefore, only activates a B-cell immune

response leading to a predominantly IgM response without an immunological memory response, as well as rapid waning of protection compared to polysaccharide conjugate vaccines (Kelly et al., 2005). The effectiveness of PPV23 in children, especially those at risk of IPD, remains controversial (Borrow et al., 2012). It is therefore advisable, that until a conjugate vaccine containing serogroup 15 becomes available, any protection afforded by PPV23, even if short-term, is likely to be beneficial in this highly vulnerable group who appear to be susceptible to some of the additional PPV23 serotypes, particularly serogroup 15.

One of the potential limitations with the review (Chapter 5) was the lack of information on compliance or adherence with penicillin prophylaxis. However, the importance of penicillin prophylaxis cannot be emphasised enough, especially in children aged <5 years, because of its potential to protect against all pneumococcal infections and not just the vaccine serotypes (Yawn et al., 2014). Children with SCD need to continue taking penicillin prophylaxis until a universal vaccine targeting all pneumococci irrespective of their capsular serotype becomes available (Ladhani et al., 2015).

9.3 **MENINGITIS**

Meningitis is the most severe clinical presentation of IPD and is associated with a significantly higher case fatality rate, with high rates of sequelae among survivors. Several countries with established pneumococcal vaccination programmes reported a differential impact of PCV on pneumococcal meningitis (Ben-Shimol et al., 2017; Alari et al., 2016; Hsu et al., 2009; Ruiz-Contreras et al., 2017; Tsai et al., 2008; Liset et al., 2015).

In chapter 7, the impact of the introduction of PCV on pneumococcal meningitis in England and Wales was assessed. This was the largest epidemiological study that described '*the effect of PCV on pneumococcal meningitis'* over a 16-year surveillance period between 2000/01 and 2015/16. There were 84,473 laboratory-confirmed IPD cases across all age groups in England and Wales, including 4,160 cases (4.9%) with meningitis. Although, large declines in IPD incidence were observed after both PCV7 and PCV13 introductions, a differential impact on pneumococcal meningitis compared to non-meningitis presentations

was observed. The annual incidence of pneumococcal meningitis remained unchanged after PCV7 introduction, but declined by 48% after PCV13 replaced PCV7, including a 70% decline in children < 5 years of age (Oligbu et al., 2019b).

In France, too, PCV7 implementation led to a rebound in the incidence of pneumococcal meningitis, with a 2.2-fold increase in childhood meningitis cases (with a 6.5 fold increase in cases among < 2 years-old) (Alexandre et al., 2010), accompanied by a 44% reduction after PCV13 replaced PCV7 (Alari et al., 2016; Cohen et al., 2016). In contrast, many other European and other countries with established PCV programmes reported a decline in pneumococcal meningitis after both PCV7 and PCV13 implementation (Imöhl et al., 2015; Ricketson et al., 2014; Moreira et al., 2016; De Oliveira et al., 2016; Polkowska et al., 2017; Ruiz-Contreras et al., 2017; Shinjoh et al., 2017; Jacobs et al., 2017).

There were also significant shifts in the serotypes causing pneumococcal meningitis over time. Prior to PCV7 implementation, serotype 14 was the most frequent serotype causing meningitis in England and Wales (Trotter et al., 2010). This was consistent with other countries including Belgium, Germany, and Brazil (Verhaegen et al., 2003; Vieira et al., 2007; Imöhl et al., 2010). During the PCV7 era, serotypes 7F and 19A, among others, emerged mainly through clonal expansion, as the most common replacing serotypes causing pneumococcal meningitis in US and Europe (Waight et al., 2015; Richter et al., 2013; Hanquet et al., 2010). However, unlike the UK, the emerging serotype 19A strains in other countries, including the US and France, exhibited high rates of resistance to multiple antibiotics (Janoir et al., 2016; Mahjoub-Messai et al., 2009). Additionally, meningitis due to serotype 7F has been associated with more severe disease in children, with increased rates of complications and a higher case fatality rate compared with other serotypes (Rückinger et al., 2009).

The replacement of PCV7 with PCV13, which offer protection against both serotypes 7F and 19A, led to a rapid reduction in IPD, including meningitis, due to these serotypes across all age groups, and consequently reduction in the strains non-susceptible to antibiotics in countries with high rates of antibiotic-resistant pneumococcal strains (Ben-Shimol et al., 2018). Currently, meningitis due to PCV13 serotypes is rare and the non-PCV13 serotypes 8 and 12F are the main replacing serotypes causing meningitis across all age groups in England

and Wales. A common feature shared among countries with established PCV13 programme is the high proportion of cases (70-80%) that are now due to non-PCV13 (Olarte et al., 2015; Levy et al., 2016; Kleynhans et al., 2019). The predominance of serotype 8, in particular appears unique to our population (Oligbu et al., 2019b). The finding of lower odds of meningitis but a higher risk of death with serotype 8 meningitis is novel (Oligbu et al., 2019b), and needs to be verified in other populations.

Pneumococcal meningitis is associated with a higher CFR compared to other clinical presentations and the CFR did not change over the years, even after implementation of two PCVs and despite significant reductions in disease incidence (Hirose et al. 2015; Ruiz-Contreras et al., 2017; Jacobs et al., 2017). This is likely to be because, although the risk of pneumococcal meningitis may be lower after PCV introduction, once meningitis develops, the outcomes in terms of long-term complications or death are similar, irrespective of the infecting serotype (Liset et al., 2015). This supports previous experimental work that suggests that death and sequalae following pneumococcal meningitis is a result of a hyperinflammatory host response to the bacteria (Meli et al., 2006).

The overall impact of PCVs on pneumococcal meningitis has been less prominent compared to other clinical presentations in England and Wales. Our findings and those of others highlight the importance of monitoring vaccine-preventable disease by their major clinical presentations. Although these vaccines are highly effective in preventing IPD caused by vaccine serotypes, the overall reduction, however, has been offset by increase in replacement disease due to non-vaccine serotypes (Ladhani et al., 2018). Because these serotypes have only emerged after the pneumococcal vaccines were introduced, there is very little knowledge of the risk, clinical severity and outcomes of pneumococcal meningitis caused by these new and emerging serotypes.

9.4 **DEATHS**

In industrialised countries, the case fatality rate for IPD is low, but little is known about the children who die of IPD. The final analysis presented in chapter 8 was the largest prospective national surveillance using multiple data sources to obtain detailed information from

clinicians on all childhood deaths attributable to IPD in England and Wales between 4 September 2006 and 3 September 2014, a period covering 8 surveillance years and 10 birth cohorts of children eligible for PCV. There were 150 IPD-related deaths from 3,146 IPD cases. The CFR of 4.8% showed that IPD in young children was rarely associated with a fatal outcome, with more than half (59%) of deaths in infants, mainly < 3months old (28%). These infants were too young to benefit from the infant immunisation programme. PCV introduction was associated with a 69% reduction in IPD-related mortality rate in children aged <5 years since the first year of the immunisation program (Oligbu et al., 2017b), but, unfortunately, this work was unable to compare with the pre-PCV7 rates, when IPD-related mortality rates were likely to be even higher, because the surveillance only began after PCV implementation in the UK

The serotypes responsible for IPD-related deaths reflected those that were circulating at the time. After PCV7 introduction in England and Wales, an increase in the additional PCV13 and other serotypes was observed (Miller et al., 2011), which was associated with an increase in LRTI presentations and a decrease in the other clinical presentations (Ladhani et al., 2013), yet nearly half the IPD-related deaths remained due to meningitis, irrespective of the pneumococcal serotype (Oligbu et al., 2017b). Population-based studies have identified significant associations between specific pneumococcal serotypes and death among patients presenting with septicaemia (Harboe et al., 2009) and pneumonia (Weinberger et al., 2010) but not with meningitis (Alanee et al., 2007).

PCVs were developed to protect against the most virulent serotypes and it was hoped that any replacing serotypes would have lower invasive potential. This assertion was partly true in that non-vaccine serotypes have only partly replaced the large niche in IPD cases left by the PCV serotypes (Waight et al., 2015; Ladhani et al., 2018). In Spain, significant declines in IPD-related mortality rates have been reported in adults following both PCV7 and PCV13 introduction (Grau et al., 2016). In children, such impact has been more difficult to demonstrate because of the smaller number of childhood cases and deaths.

A major risk factor for death in children with IPD was the presence of underlying comorbidities. Previous reports following PCV7 introduction have supported these findings,

in addition to meningitis as independent risk factors for death in children with IPD (Wang et al., 2019; Ladhani et al., 2013; Ladhani et al., 2012). IPD-related CFR was 9.1% in children with comorbidities compared with 3.5% in those without (Ladhani et al., 2013). The work presented in this thesis has shown that, a third of fatal cases had an underlying comorbidity compared to an overall prevalence of 15% among children with IPD after PCV7 introduction, with malignancy/immunosuppression and congenital heart disease predominating (Ladhani et al., 2013). Further, the fact that more than one-third of children (mainly infants) died outside the hospital or in the emergency department suggests either a very rapid onset or parental failure to recognise the warning symptoms and signs of serious infection. Raising awareness may improve earlier recognition of the sick child, leading to earlier treatment with better outcomes.

9.5 **Summary and Clinical Implication**

The introduction of PCVs has had a major impact on pneumococcal disease in young children, additional impact was observed in adult because of herd effects but to a variable extent. This thesis has demonstrated that these vaccines were highly effective in reducing vaccine type IPD and most cases are now due to non-PCV13 serotypes, which are now associated with higher comorbidity prevalence. A change in clinical presentation following vaccine introduction was also observed. Reassuringly, vaccine failures and fatality following IPD remain low, with serotypes 3 and 19A isolated in majority of the failure cases; this is not surprising as these two serotypes had the lowest immunogenicity as well as the lowest vaccine effectiveness estimates among PCV13 serotypes (Andrews et al., 2014). In addition, recent carriage studies suggests these 2 serotypes have the highest carriage among the vaccine serotypes since the introduction of conjugate vaccines (Southern., et al. 2018). It is therefore possible that the current PCV13 will continues to provide some immunity against disease caused by these persisting PCV13 serotypes in vaccinated children but not capable of providing indirect (herd) protection to the population or prevent carriage. Other industrialised countries with established PCV13 programmes have also been unsuccessful in controlling these serotypes (Hanquet et al., 2019; Balsells et al., 2017).

However, children with sickle cell disease continue to be at higher risk of IPD and fatalities despite all the available interventions compared with other children with comorbidities, and

serogroup 15 was responsible for majority of IPD in this cohort. The differential increase in fatality in this cohort could be adduced to the hypothesis that serotypes with a low invasive potential often associated with a higher fatality in those with underlying condition (Brueggemann etal., 2003; Zemlickova., et al. 2010). In the study by Makwana and colleague, using the same cohort, children with sickle cell disease, were more likely to die of IPD compared with other forms of immunosuppression, including malignancy, especially among 24- to 59-month olds. Interestingly, this age group, when compared with children without comorbidity, the CFR was remarkably similar (Makwana et al., 2018). This reassuring finding is likely to be a result of rapid access to medical care for immunosuppressed children presenting with fever and strict protocol adherence with low threshold for initiating antimicrobial therapy by clinicians (NICE., 2012). It is therefore possible that with improved rapid access to healthcare facilities by children with SCD when they become sick and maintaining high adherence to penicillin prophylaxis, there could be a reduction in CFR in children with SCD.

Among the different forms of IPD, meningitis remains an independent risk factor for death, with non-PCV serotypes, especially serotypes 8, 12F, and 22F now responsible for the majority of cases. The effect of these serotypes on mortality remained questionable, but this work found serotype 8 more likely to cause fatality in this cohort despite a low carriage rate (Southern et al., 2018). This finding is yet to be corroborated in other studies. Other recent studies have been unable to identify any differences in the clinical characteristics of children with pneumococcal meningitis even though cases due to PCV13 serotypes declined rapidly after PCV13 introduction and those due to non-PCV13 serotypes increased (Olarte et al., 2015)

However, compared to other conjugate vaccines, such as *Haemophilus influenzae* type b (Hib) and group C Meningococcal (MenC), the control of IPD through vaccination has been more challenging and the overall benefits of the current PCVs is likely to decline in the developed countries because of serotype replacement disease, but will continue to have a major impact in developing countries where most pneumococcal deaths still occur.

9.6 **Conclusions**

The childhood pneumococcal vaccination programme has led to a significant reduction in the incidence of invasive pneumococcal disease, including meningitis, across all age groups through a combination of the direct and indirect protection offered by the national immunisation programme with high vaccine uptake. However, compared to other clinical presentation, there was a lower than expected impact on pneumococcal meningitis, with case fatality rates due to meningitis remaining relatively unchanged across the age groups.

This thesis has also demonstrated that these PCVs are highly effective in preventing IPD due to the respective vaccine serotypes. The rate of PCV failure, irrespective of the vaccine used or schedule, was very low, as was CFR in children with PCV failure. Most children with PCV13 failure were healthy, developed LRTI, and survived their infection without long-term complications. The continuing low prevalence of PCV7 failures after PCV13 introduction is reassuring and it is likely that PCV13 failure will also decline in the coming years.

However, children with SCD remained at a very high risk of pneumococcal disease and death despite these measures of daily penicillin prophylaxis as well as pneumococcal vaccination. The majority of serotypes causing IPD in children with SCD are no longer vaccine preventable, therefore every effort should be made to ensure that these children adhere to penicillin prophylaxis and pneumococcal vaccines. Further studies should assess whether improving parental education to seek early medical help might also achieve better outcomes.

Finally, given that most IPD cases, including meningitis are now due to non-PCV13 serotypes, including most fatal IPD cases, additional strategies will be required to reduce childhood pneumococcal deaths in countries with established pneumococcal vaccination programmes. Further studies are therefore needed to assess the risk factors, clinical course and outcomes of pneumococcal meningitis due to these replacing serotypes. Meanwhile, alternative strategies such as protein-based serotype-independent will be needed to curb the problem of serotype replacement disease.

CHAPTER 9

Future steps

This chapter will detail research I intend to conduct over the next 4 years of my career and build on work described earlier in this thesis. I will outline a series of research questions that have arisen through this thesis and detail studies that attempt to address these.

10.1 Characteristics of Children with Pneumococcal Meningitis in the United Kingdom and Republic of Ireland

10.1.1 Research question

What is the clinical burden (rate of hospitalisation including PICU admission) of pneumococcal meningitis in the United Kingdom and Republic of Ireland?

Is this era of non-vaccine serotypes, what are the characteristics of children with pneumococcal meningitis?

This grant (Sir Peter Tizard bursary - received) is offered to junior paediatric consultants to conduct a national British Pediatric surveillance (BPSU) study after a national competition. This proposed study builds on the findings from the epidemiological study of pneumococcal meningitis in the UK (Chapter 7) and childhood deaths following the introduction of conjugate vaccines (Chapter 8).

10.1.2 Background

The introduction of pneumococcal vaccines have been associated with a rapid decline in pneumococcal disease, including meningitis caused by the vaccine serotypes (Waight et al.

2015; Oligbu et al., 2019). However, the overall reduction, has been offset by a small increase in disease due to non-vaccine serotypes (Miller et al., 2011; Oligbu et al., 2019b). Currently, nearly all pneumococcal infections in children are caused by non-vaccine pneumococcal serotypes. Since these serotypes have only emerged after the pneumococcal vaccines were introduced, there is very little knowledge of the risk, clinical severity and outcomes of pneumococcal meningitis caused by these new and emerging serotypes.

This study will aim to understand the clinical severity, presenting features, acute management, clinical course and outcomes of this replacing serotypes causing meningitis. The results will be compared with the national standard of care for children with serious infections.

10.1.3 Research plan

Study design

Prospective observational cohort study.

Primary outcome measures

- To estimate the incidence of childhood pneumococcal meningitis in children aged <16 years in the UK and Republic of Ireland in the era of pneumococcal conjugate vaccines.
- Describe the characteristics of children with pneumococcal meningitis.

Inclusion Criteria:
Any child aged <16 years with CSF positive for pneumococcus by culture and/or PCR.

Exclusion Criteria
Children who do not fulfil the inclusion criteria.

10.1.4 Methodology

Paediatricians will be asked to notify any case of pneumococcal meningitis in the previous month through the BPSU orange card system. Paediatricians notifying a case will be asked to complete a detailed questionnaire about the case. The questionnaire will also request

information about the infecting pneumococcal serotype, which should be known to the paediatrician. If this is not the case, then the study team will ask the paediatrician to contact the local microbiology team or, if needed, the respective national reference laboratory in each of the nations for the information.
Pneumococcal meningitis cases identified through national surveillance in place within individual nations will be used as an alternate data source to estimate the total burden of disease in the UK and Ireland.
For the 12-month follow-up, we will send a standard questionnaire to the paediatricians reporting a case of pneumococcal meningitis through the BPSU to assess possible long-term complication following pneumococcal meningitis.

10.1.5 Potential benefit

Understanding the disease caused by these new, emerging non-vaccine serotypes, will enable pediatricians to provide parents of children with pneumococcal meningitis a more accurate picture of the course of illness and long-term prognosis.

It will also allow for a better estimation of the burden of childhood pneumococcal meningitis in the individual nations and across the UK and Ireland by linking multiple data sources. In terms of service benefit, the results will be compared with the national standard of care for children with serious infections with the aim of identifying areas of improvement to achieve better outcomes. The study results are likely to inform future pneumococcal vaccine policy.

10.2 Neurodevelopmental Outcomes of pneumococcal meningitis in children

10.2.1. Research question

Are the newly emerging serotypes more likely to cause severe disease and neurological complications compared to the vaccine serotypes?

This is a follow-on study from the one outlined above using the same cohort. A grant application has been made to Meningitis Research Foundation. This proposed study also builds on the findings of the effect of PCV on pneumococcal meningitis in Chapter 7.

10.2.2 Background

Survivors of pneumococcal meningitis (PM) are more likely than any other causes of meningitis to suffer from neurological and other serious long-term complications (Dery and Hasbun., 2007; Neuman and Wald., 2001; Epstein et al., 1992). In a meta-analysis including 48 studies, 32% had long-term complications, including hearing loss, seizures, brain injury and blindness (Jit., 2010). A number of studies have reported long-term effect of other common bacterial causes of meningitis and health-related quality of life (HRQoL) outcomes, including physical, emotional, psychological, social, and overall well-being of sufferers of bacterial meningitis (Olbrich et al., 2018; Giorgakoudi et al., 2018) (Oostenbrink et al., 2002), but studies on pneumococcal meningitis are lacking in the UK, particularly in this era of this new and emerging serotypes. Thus, this area of research has been identified as an area in need of further and more recent evidence. Such evidence on the long-term consequences of pneumococcal meningitis in terms of quality-adjusted life-years (QALYs) for both survivors and carers will be valuable in modelling the impact of preventive interventions in children at risk.

10.2.3 Research plan

Study design

Prospective observational cohort study.

Primary outcome measures

- Identify the long-term neurological sequelae (neurodevelopment outcomes) of meningitis survivors.
- Assess health related quality of life of survivors and caregivers.
- Compare outcome with available data prior to the introduction of conjugate vaccines and with other common bacterial causes of meningitis.

10.2.4 Methods

My study proposes to follow-up a cohort of 100 children affected by pneumococcal meningitis (aged < 2 years) recruited through the above BPSU national pneumococcal meningitis surveillance study (Project 257619) due to start in January 2020 in collaboration with over 20 years of PHE established pneumococcal surveillance. Additional individual parental consent will be obtained from affected families. Affected children will be followed up after 12 months of the illness.

It is proposed that two aspects of long-term sequelae be assessed: neurodevelopmental impairment and quality of life.

The Bayley Scales of Infant Development (BSID-III) is a standard series of measurements used primarily to assess the motor (fine and gross), language (receptive and expressive), and cognitive development of infants and toddlers, ages 0-3. Raw scores of successfully completed items are converted to scale scores and to composite scores. At the completion of the test the assessor will provide a report on the test, including in addition to the scores, comments on the test conditions and any other factors that may have influenced the outcomes of the test.

At the time of these visits, parents will also be asked to complete the Infant and Toddler Quality of Life Questionnaire (ITQOL) of children between 2 months and 5 years old. This well-validated questionnaire provides a comprehensive assessment of health status and health-related quality of life, including physical, psychological and social domains (Landgraf et al., 2013). The ITQOL consists of 103 items (10 multi-item scales and 2 single-item scales) that generally refer to the situation during the past 4 weeks. Per scale, the items that have 4, 5 or 6 response options are summed up with equal weight per item and transformed into a 0 (worst possible score) to100 (best possible score) scale.

Data obtained from the above BPSU study will be linked with this study and this will enable assessment of the relevance and significance of the information obtained from the BPSU study to their long-term outcomes.

10.2.5 Potential benefit of the study

Understanding the neurodevelopment outcomes and clinical burden caused by these new, emerging non-vaccine serotypes, will enable paediatricians to provide parents of children with pneumococcal meningitis a more accurate picture of the long-term prognosis. The study results are likely to inform future pneumococcal vaccine policy and shape healthcare delivery to affected families.

10.3 Recurrent IPD in Children

10.3.1 Research Question

What are the characteristics of children with recurrent invasive pneumococcal diseases?

This proposed study builds on work outlined in chapters 3 and 4.

10.3.2 Background

Certain clinical conditions have been associated with increased risk of IPD, for example, children with sickle cell disease (SCD), those with human Immunodeficiency Virus (HIV) infections, asplenia, nephrotic syndrome, immunodeficiency other than HIV, children on immunosuppressive therapy and conditions associated with cerebrospinal fluid leak (van Hoek et al., 2012). In addition, primary immunodeficiency diseases, especially children with complement deficiencies and B-cell dysfunction have been reported to have a high risk of IPD (Ram et al., 2010).

Although type-specific immunity results from prior infection, recurrent infections by the same pneumococcal type can occur, especially in immune-compromised hosts. It is estimated that 2.3% to 4.4% of IPD cases are due to recurrent infection, and more than half (52% to 92%) of these occur in children with underlying comorbidity (Einarsdottir et al., 2005; Mason Jr et al., 2007; King et al., 2003).

In this study, the work will aim to describe the clinical characteristics and serotype distribution of children with recurrent IPD in our pediatric population, as well as identify the underlying risk factors.

10.3.3 Research plan

Study design

Prospective enhanced national surveillance study.

Primary outcome measures

- Describe the clinical characteristics of children with recurrent IPD.
- Identify underlying risk factors for recurrent IPD.

Case Definition

A recurrent IPD was defined as 2 or more episodes of IPD in the same individual at least one month apart. Among recurrent IPDs, relapse will be differentiated if the same pneumococcal isolate is identified (defined as 2 strains with the same clonal type and/or serotype) and reinfection IPD if it is different (defined as 2 strains with different serotype and/or clonal type).

10.3.4 Methods

Eligible children will be identified using PHE LabBase2 database (PHE's national database). National Health Service (NHS) laboratories in England and Wales electronically report all significant infections to PHE and routinely submit all invasive pneumococcal isolates to the PHE national reference laboratory for confirmation and serotyping (Waight et al., 2015). As part of enhanced national surveillance, general practitioners and hospital pediatricians for <5 year-olds with laboratory-confirmed IPD completed a short questionnaire on vaccination history, known comorbidities at the time of IPD, complications, and outcomes. Completed questionnaires from general practitioners will be returned to PHE Colindale. Data on children with recurrent infection will be retrieved for analysis.

10.3.5 Potential benefit

This surveillance will better estimate the burden of recurrent invasive childhood pneumococcal infection in England and Wales, and also identify areas of improvement in terms of management of these cases and to achieve better outcome.

Understanding the risk factors will enable pediatricians to provide parents of children with some preventative measures.

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Appendix 1: Search Strategy on PCV Failure in Children: A systematic review of the literature

Database: Embase

Search for: limit 17 to (English language and yr="2000 -Current")

Search Strategy:

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1 ((vaccin* or immuni?ation) adj3 fail*).mp. [mp=title, abstract, heading word, drug trade name, original title,
device manufacturer, drug manufacturer, device trade name, keyword]

2 (invasive pneumococcal disease or streptococcal pneumonia or IPD or vaccine type disease).mp. [mp=title, abstract,
heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

3 ((vaccin* or immuni?ation) adj3 (timeline or timetable or schedule)).mp. [mp=title, abstract, heading word, drug
trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

4 (PCV7 or PCV10 or PCV13 or PCV9).mp. [mp=title, abstract, heading word, drug trade name, original title, devicemanufacturer, drug manufacturer, device trade name, keyword]

5 (7-valent or 10-valent or 13-valent or 9-valent).mp. [mp=title, abstract, heading word, drug trade name, originaltitle, device manufacturer, drug manufacturer, device trade name, keyword]

6 (child* or youth* or toddler* or teen* or young adult or adolescen* or baby or babies or infan* or paediatric* orpediatric*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drugmanufacturer, device trade name, keyword]

7 exp immunization

8 child

9 infant

10 adolescent

11 exp Pneumococcus vaccine

12 exp pneumococcal infection

13 1 or 2 or 12

14 3 or 7

15 4 or 5 or 11

16 6 or 8 or 9 or 10

17 13 and 14 and 15 and 16

18 limit 17 to (english language and yr="2000 -Current")

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

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1 exp Vaccination

2 ((vaccin* or immuni?ation) adj3 fail*).mp. [mp=title, abstract, original title, name of substance word, subjectheading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, uniqueidentifier]

3 (invasive pneumococcal disease or streptococcal pneumonia or IPD or vaccine type disease).mp. [mp=title, abstract,original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word,rare disease supplementary concept word, unique identifier]

4 ((vaccin* or immuni?ation) adj3 (timeline or timetable or schedule)).mp. [mp=title, abstract, original title, nameof substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare diseasesupplementary concept word, unique identifier]

5 exp Immunization Schedule

6 (PCV7 or PCV10 or PCV13 or PCV9).mp. [mp=title, abstract, original title, name of substance word, subject headingword, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, uniqueidentifier]

7 (7-valent or 10-valent or 13-valent or 9-valent).mp. [mp=title, abstract, original title, name of substance word,subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary conceptword, unique identifier]

8 (child* or youth* or toddler* or teen* or young adult or adolescen* or baby or babies or infan* or paediatric* orpediatric*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word,protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

9 exp child/ or exp infant

10 exp Adolescent

11 exp Pneumococcal Vaccines

12 exp Pneumococcal Infections

13 8 or 9 or 10

14 6 or 7 or 11

15 2 or 3 or 12

16 4 or 5

17 13 and 14 and 15 and 16

18 limit 17 to yr="2000 -Current"

19 limit 18 to English language